1. Obviousness-Type Double-Patenting Rejection:

Claims 14-22 are provisionally rejected under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claims 1, 2, 4-12, 24 and 29-33 of copending U.S. Patent Application No. 08/483,944. The Examiner has indicated that this provisional rejection can be overcome by timely filing a Terminal Disclaimer.

As noted in the previous Amendment, Applicant respectfully requests that this provisional rejection be held in abeyance until the other outstanding rejection is withdrawn.

2. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-5, 7-10, 12-22 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner has stated that while the specification as filed is enabling for the use of glycyldioctadecylamide for lipidizing proteins in order to achieve intracellular localization of the lipidized protein, the specification allegedly does not enable the use of any other lipid having a hydrocarbon tail of greater than 12 carbons for making lipidized proteins that localize intracellularly. In support of this rejection, the Examiner cites Horan *et al.* (U.S. Patent No. 5,665,328), and states that it is unpredictable whether lipidized proteins that contain a hydrocarbon tail of more than 12 carbons will localize intracellularly.

Applicant respectfully traverses this rejection. Undue experimentation would ***not*** be required to make or use any lipidized proteins with a hydrocarbon tail of at least 12 carbons that can localize intracellularly. The proper test of enablement is "whether one skilled in the art could make or use the claimed invention without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); MPEP §2164.01.

Applicant herein provides a declaration of Dr. Bernard Malfroy-Camine, a named inventor of the present application, and an expert in the field of development of therapeutic agents directed against intracellular targets (*see*, Dr. Malfroy-Camine's *curriculum vitae* which is attached to his declaration as Exhibit A). As stated by Dr. Malfroy-Camine in his declaration, Horan *et al.* does ***not*** support the Examiner's allegation that it is unpredictable

whether any lipidized proteins that contain an added hydrocarbon tail of greater than 12 carbons will localize intracellularly. Moreover, as stated in Dr. Malfroy-Camine's declaration, the specification, coupled with the information known in the art at the time the invention was made, provides ample guidance for one of skill in the art to make and use the claimed invention ***without*** undue experimentation.

a. Horan et al. Does Not Support Unpredictability of Intracellular Localization of Lipidized Proteins with Hydrocarbon Tail of Greater than 12 Carbons

The Examiner has raised a concern as to whether lipidized proteins with a hydrocarbon tail of greater than 12 carbons can localize intracellularly based on Horan *et al.* As stated by Dr. Malfroy-Camine in his declaration, it may be helpful to clarify the description in Horan *et al.* relied upon by the Examiner. Horan *et al.* generally describes bio-affecting compounds having a hydrocarbon substituent for binding *to the cell membrane surface* (*see, e.g.*, col. 3, lines 25-42). By contrast, the present invention describes lipidized proteins with a lipid substituent having a hydrocarbon tail of at least 12 carbons that are capable of transvascular transport, enhanced organ uptake *and intracellular localization*. Thus, the problem being solved by Horan *et al.* differs completely from that of the present invention.

Moreover, as stated by Dr. Malfroy-Camine in his declaration, Horan *et al.* does ***not*** state that it is unpredictable whether lipidized proteins that contain an added hydrocarbon tail of greater than 12 carbons will localize intracellularly. Rather, Horan *et al.* was concerned with determining a suitable hydrocarbon tail length for binding a bio-affecting compound with the hydrocarbon tail *to the cell membrane surface*. For example, Horan describes that the number of linear carbons in the hydrocarbon tails of the compounds together with the chemical nature of the bio-affecting moiety are important factors in achieving binding of the compounds to the cell membrane surface (*see,* col. 3, lines 52-56). Horan *et al.* further states the following:

> Experience with use of cyanine derivatives as diagnostic agents indicates that hydrocarbon tails of less than 3 carbons causes the cyanine to penetrate the plasma membrane and the nuclear membrane of cells resulting in staining of RNA and DNA. If carbon tails have a length greater than 3 carbons and less than 12 carbons, the compound no longer binds RNA and DNA but

> responds to membrane potential and enters the mitochondria... When the sum of the linear carbons in the hydrocarbon tail(s), is 23 or greater the lipophilicity of the molecule is increased such that it is retained in the plasma membrane and will not leak or transfer to other cells.... Thus, there may be a practical limitation on the length of the hydrocarbon tail(s) *depending on the chemical nature of the bio-affecting moiety to which it is to be bound.* [Emphasis added]. *See* col. 3, line 56 to col. 4, line 12.

As shown in the emphasized passage, the length of the hydrocarbon tails suitable for binding the bio-affecting compounds to cell membrane surface depends on the chemical nature of the bio-affecting moiety to which it is bound. Therefore, Horan *et al.* does not support the Examiner's statement that it is unpredictable whether any lipidized proteins that contain an added hydrocarbon tail of greater than 12 carbons will localize intracellularly.

In fact, the present specification provides a working example that a lipidized protein with a hydrocarbon tail of greater than 12 carbons, namely glycyldiooctadecylamide, is capable of localizing intracellularly. For example, glycyldiooctadecylamide was linked to bovine IgG (*see,* Example 1 at pages 30-31 of the specification). This lipidized protein was labeled with ^{14}C, and was administered intravenously to mice. It was shown that the lipidized proteins were uptaken by various organs, such as brain, liver, spleen and kidney. In another example, a monoclonal antibody that specifically binds to Tat protein of HIV-1 was lipidized with glycyldiooctadecylamide (*see,* Example 2 at page 32-33 of the specification). It was shown that when cells were pretreated with the lipidized anti-Tat antibody prior to addition of HIV-1 virus, the treated cells were almost completely protected from the cytopathic effects of the HIV-1 virus. By contrast, cells that were treated with native anti-Tat antibody or that were untreated were not protected from the cytotoxic effect of the HIV-1 virus. These results indicate that lipidized proteins with a hydrocarbon tail of greater than 12 carbons can localize intracellularly.

b. The Specification Provides Ample Guidance for Making and Using Other Lipidized Proteins with a Hydrocarbon tail of At Least 12 Carbons

As stated by Dr. Malfroy-Camine in his declaration, the specification also provides ample guidance for making and using other lipidized proteins with a lipid substituent having a hydrocarbon tail of at least 12 carbons for intracellular localization. For example, any lipids such as lipoamines, lipopolyamines, and fatty acids can be attached by a covalent linkage to a carbohydrate side chain of a protein (*see* page 15 lines 25-29 of the specification). As an illustration, lipoamines with varying lengths of hydrocarbon chains are described at pages 17-18 of the specification. Methods for attaching these various lipid substituents to proteins are described in, *e.g.*, page 18, lines 30-32 and in Example 1 of the specification. Importantly, the present specification also provides a variety of methods for testing whether a lipidized protein localizes intracellularly. For example, as described above, lipidized proteins can be radiolabeled, and their uptake by organs can be evaluated (*see*, *e.g.*, page 31 of the specification). In another example, a lipid substituent can be attached to an anti-Tat antibody, and its ability to protect cells from HIV-1 virus infection can be evaluated (*see*, *e.g.*, pages 32 and 33 of the specification). In view of this and other portions of the specification, coupled with information known in the art, one of skill in the art would have been able to make and use other lipidized proteins and readily determine which lipidized proteins will localize intracellularly without undue experimentation.

c. 35 U.S.C. §112 Does Not Require that Applicant Predicts, A Priori, Which Lipidized Proteins Will Localize Intracellularly

Finally, the Examiner is reminded that Applicant is not required to predict, *a priori*, which lipidized proteins will localize intracellularly or not. The key issue under 35 U.S.C. §112, first paragraph, is whether or not undue experimentation is required to make or use the claimed invention. As explained by the Court of Customs and Patent Appeals,

> [i]f the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction*, whether the claimed product will be obtained" (emphasis in original), as the dissent claims, then all "experimentation" is "undue," since the term "experimentation" implies that the success of the particular activity is *uncertain*.

> Such a proposition is contrary to the basic policy of the Patent Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

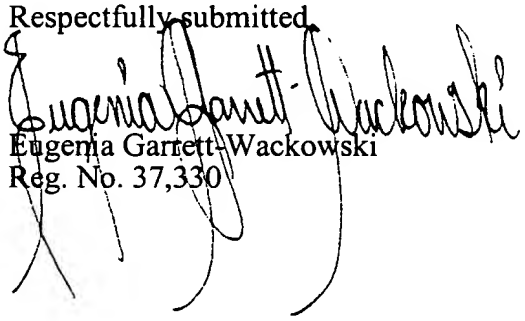
Assuming *arguendo* that one would not have been able to predict whether certain lipidized proteins will localize intracellularly, the alleged lack of predictability does not render a claim invalid under 35 U.S.C. §112 unless "undue" experimentation is required to make the claimed products. As explained above and as explained by Dr. Malfroy-Camine in his declaration, ***no*** undue experimentation would be required to practice the invention as claimed. Accordingly, the rejection is improper.

In conclusion, there is no compelling objective basis to believe that lipidized proteins with a lipid substituent other than glycyldiooctadecylamide will not localize intracellularly. Given the working example and ample guidance provided in the specification, one of skill in the art would have been able to make and use a numerous other lipidized proteins having hydrocarbon tails of at least 12 carbons ***without*** undue experimentation. Accordingly, the rejection is improper and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (925) 472-5000.

Respectfully submitted,



Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
EGW:lls